As will be discussed in greater detail hereinbelow, that statement is incorrect. Because that incorrect statement is the foundation of the rejection, the rejection is flawed and cannot stand.

An orogastric tube is as the descriptive name states, a tube that is configured to traverse the mouth and to end in the stomach. An orogastric tube is analogous to a nasogastric tube that runs through a nostril into the stomach. An orogastric tube generally is used for "tube feeding" via the mouth. Generally, the combining form of the word descriptive of the intestine is "entero" such as enterostomy, which is an opening into the intestine. Thus, an orogastric tube does not run into the intestine.

Moreover, because a function of the intestine is absorption, it stretches the imagination that a tube would be instilled into the intestine to deliver a pharmaceutical for use in a host if less invasive means are available. Thus, a known parenteral means of delivery, such as intravenous delivery, is the most likely and more efficient means of introducing a pharmaceutical into a host. An oral means is preferred to avoid a parenteral means and an invasive non-parenteral means, such as an enterostomy.

That is a purpose of the instant invention, that is, finding a least invasive means for gene delivery. Thus, while a tube was used in the working examples, the instant specification teaches making ingestable forms of a drug containing AAV. Running a tube via the mouth into the intestine would defeat the purpose of finding a non-parenteral means and particularly a non-invasive non-parenteral means of gene delivery.

At the bottom of page 2 of the Office Action, the Examiner concluded that outside of the working examples, no other working applications of the instant invention are enabled.

A working example is not a sine qua non of satisfying the Patent Statute. An application need not contain that which is known in the art. The artisan is charged with the knowledge available in the art at the time of the invention. The instant invention relates to use of AAV. The instant invention relates to the non-parenteral administration of AAV. The art of non-parenteral, such as, oral administration of pharmaceuticals is well settled. Nevertheless, the instant specification presents a detailed teaching of how to make non-parenteral formulations.

Beginning halfway down page 3 of the Office Action, the Examiner relied on Page et al. for the proposition that gene delivery strategies have concentrated on the parenteral route and oral administration has been largely ignored. Then several reasons for that decision are explained, essentially relating to the harsh environment of the stomach.

Page & Cudmore is a review article that instead promotes the advantages of AAV as a vehicle for delivery of genes to the gastrointestinal tract, see section bridging pages 97 and 98. The one possible disadvantage of AAV noted in Table 2 of Page & Cudmore is that of packaging capacity, however, as noted at the bottom of page 97, right column, Page & Cudmore note that the size limitation had already been overcome.

A goal of the instant invention is to find a facile means of delivering AAV to a host. The instant invention relates to the use of AAV as the vector choice. AAV is acutely suitable for non-parenteral administration because as was well known in the art, AAV is a very stable particle resistant to temperature and pH extremes as well as to many solvents.

Thus, the issues raised by Page & Cudmore relating to pH and the hostile environment of the stomach are of no relevance to the instant invention because AAV is known to be resistant and can survive in the gastric environment.

The Examiner stated about a third of the way down on page 4 of the Office Action that the level of skill in the art of oral gene delivery was considered unpredictable.

Prior to the instant invention, that might have been true. However, the instant invention directed to the use of AAV solves that problem and makes certain the oral delivery of a gene. The use of AAV removes the alleged unpredictability because of the stability of the AAV particle to the stomach environment.

In the paragraph bridging pages 4 and 5 of the Office Action, the Examiner again stated that the instant invention is limited to use of an orogastric tube for delivery to the proximal intestine.

Nothing could be further from the truth. As noted in the teachings at page 9 et seq., a number of different ways for non-parenteral administration of AAV are taught. Any of the known means for non-parenteral delivery can be used in the practice of the instant invention. A detailed teaching is provided in the instant specification even though the formulation of non-parenteral forms is well known in the art. Various known pharmaceutically acceptable carriers, diluents and excipients can be used to produce pills, capsules and the like to enhance delivery of AAV to the intestine because those pharmaceutically acceptable carriers, diluents and excipients can serve as mechanical barriers over and above the inherent resistance of the AAV particle per se to the various assaults raised by the Examiner.

In the paragraph bridging pages 4 and 5 of the Office Action, the Examiner took the position that administration was to the proximal end of the intestine, referring to page 11 of the instant specification.

As mentioned hereinabove, it is well settled, and by definition, that an orogastric tube terminates in the stomach. Thus, it is a misinterpretation that the tube bypasses the stomach and is delivered directly into the intestine.

Referring to page 11 in the instant specification as noted at lines 29 and 30, a recombinant AAV carrying a transgene was delivered to the proximal intestine using a peroral route. The definition of peroral is by the mouth. There is no mention on page 11 of an orogastric tube. The vector was found to be expressed in the cells of the proximal intestine. That is clear and any other interpretation is one that lacks objectivity.

The Examiner then stated that essentially anatomic and physiologic barriers such as mucus, gastric acidity and the like would prevent successful delivery and use of an AAV vector.

That position is without foundation because the instant specification teaches the successful use of AAV by a peroral route. Moreover, the instant specification teaches a formulation without the benefit of a carrier, diluent or excipient that provides a mechanical barrier. Instead the virus particle per se was administered. A noted at lines 2-5 on page 10 of the instant specification, simply dissolving the AAV vector in phosphate buffered saline has been demonstrated to be sufficient for successful expression of cells in the gut following peroral administration.

The instant specification and publications teaching the instant invention have demonstrated successful delivery of genes to various cells in the body of a host following peroral administration. The instant method has demonstrated that oral administration of AAV can lead to successful infection of cells of the gastrointestinal tract. Hence, the position of the Examiner is without merit.

Referring to During et al., the Nature Medicine publication of record, an orogastric tube was used and as noted in the first full paragraph in the left column on page 1135, rats were fed by oral gavage. Gavage is a forced feeding wherein food is deposited in the stomach, as practiced in the instant specification. As noted in Page & Cudmore, the During et al. Nature Medicine publication appears to be the first publication teaching peroral use of AAV.

Page & Cudmore also refer to a second During et al. publication in Science (2000) 287:1453-1460, relating to an AAV oral vaccine with efficacy in treating stroke and epilepsy. The NR1 subunit of the NMDA receptor expressed by the rAAV elicited autoantibodies thereto that exhibited a protective effect on the host.

Beginning on page 5 of the Office Action, the Examiner then relied on Rubanyi.

However, Rubanyi mentions at the top of page 115 thereof the successful treatment of hemophilia B in human patients receiving factor IX gene therapy delivered by AAV (Kay et al.). Also, as Rubanyi is a review article, it is noted on page 117 thereof that AAV is in early clinical evaluation and thus, essentially the conclusions of Rubanyi do not apply to AAV.

The publication of Kay et al. (Nature Genetics 24:257-261, 2000) referred to on page 115 of Rubanyi is evidence that the conclusions of Rubanyi do not relate to AAV. For example, in the excerpt reproduced by the Examiner, Rubanyi opines that the more promising areas of gene therapy are hemophilias and cardio-vascular diseases because of the relative ease of access for blood vessels for gene therapy. However, Kay et al. teach the successful gene therapy of hemophilia using AAV.

Because the Examiner founded his position on an improper conclusion as to the enabling disclosure, the rejection is improper. The instant application teaches any non-parenteral route of administration of AAV. AAV is a distinctive feature of the instant invention that carries with it, in part, the patentability of the instant invention, for example, the features that distinguish the instant invention over the references relied on by the Examiner as well as the hypothetical position taken by the Examiner.

Beginning at the bottom of page 7 of the Office Action, the Examiner responded to arguments previously filed.

It is noted that the cases cited by Applicant were relied on for the general proposition of what the law holds as the test for an enabling disclosure. It is believed the Examiner argued particular facts to distinguish the cases, however, Applicant relied on the cases merely for providing guidance as to a general legal tenet discussed therein.

In the last sentence on page 8 of the Office Action, contrary to the position of the Examiner, the instant invention relies in part on the use of AAV as a gene delivery vehicle and the non-parenteral delivery of the AAV. The instant application teaches the successful use of AAV by a non-parenteral route to obtain successful transformation of cells. The record also contains references to subsequent publications teaching same.

With respect to the evidence supporting successful use of AAV for gene therapy, the specification teaches successful use of AAV by non-parenteral delivery means and the publications of record support that position.

The Examiner referred to Hohlweg & Dorfler to support the position that there is no evidence of expression of oral administered genes.

However Hohlweg & Dorfler is irrelevant because those experiments relied on administration of naked DNA in the form of plasmid DNA or soybean leaves and not to administration of a virus, and particularly a virus such as AAV with a very hardy capsid shell that is resistant to the stomach environment.

With respect to item 3 discussed at the top of page 9 of the Office Action, the point is that AAV infects a wide range of cells and references were provided merely to support that position. It has been found that an orally administered AAV can infect esophagus cells and the record demonstrates that progenitor stem cells, enterocytes and lamina propia cells are transformed, see Page & Cudmore, page 97, right column, third full paragraph as well as During et al. of record. Finally as noted in During et al., Nature Medicine, page 1131, right column, lines 13-16, it was known that AAV was found in GI tract secretions and thus, cells of the GI tract are natural host cells for AAV.

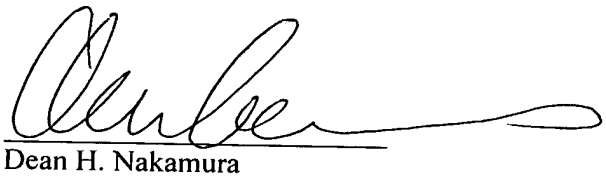
Again, a key feature of the instant invention is the use of AAV as the vehicle for gene delivery. AAV can survive in all parts of the GI tract. That observation enables the non-parenteral administration of AAV. Moreover, the instant specification and the references of record teach that AAV is successful in gene therapy and that non-parenteral delivery of AAV has led to delivery of transgenes to a variety of cells in the GI tract.

All of the issues raised by the Examiner have been found to be incorrect, irrelevant or traversed. Hence, as to the claimed invention relating to the use of AAV and delivery thereof by

non-parenteral means, the Examiner has not made a prima facie case of non-enablement as to that claimed invention. Accordingly the rejection is improper and must be removed.

Accordingly, withdrawal of the rejection and early indication of allowance are requested respectfully. If any questions remain, the Examiner is urged to contact the undersigned at the local exchange noted herein below. The Commissioner is hereby authorized to charge Deposit Account No. 18-2220 if any additional fees arise from the filing of the instant Request for Reconsideration.

Respectfully submitted,



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